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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,068	11/14/2003	Meng Yang	312762002710	2630

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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	PAPER NUMBER
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,068	YANG ET AL.	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,39 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/27/2008 has been entered.

Status

This application has been reassigned to Examiner Samuel Woolwine, whose contact information appears at the conclusion of this Office action.

The rejections made under 35 U.S.C. 103(a) in the Office action mailed 07/21/2008 are withdrawn in view of Applicant's amendment, limiting to a mammalian animal. Link et al taught C. elegans, which is not a mammal.

Any previous rejections not appearing in this Office action are considered withdrawn as no longer applicable.

Response to Arguments

Applicant's arguments with respect to claims 37, 39 and 40 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Contag et al (US 5,650,135 prior art of record) in view of Okabe et al (FEBS Letters 407:313-319; 1997).

With regard to claim 37, Contag taught (column 25, line 25):

"Alternatively, an animal model for the study of putative anti-inflammatory substances can be made by making the animal transgenic for luciferase under the control of the E-selection promoter. Since E-selection is expressed at sites of inflammation, transgenic cells at sites of inflammation would express luciferase.

The system can be used to screen for anti-inflammatory substances. Inflammatory stimuli can be administered to control and experimental animals, and the effects of putative anti-inflammatory compounds evaluated by their effects on induced luminescence in treated animals relative to control animals."

This passage suggested *administering a test substance to said animal which expresses a* [light generating protein] *under the direction of a promoter of an endogenous gene, and determining the expression of said promoter via observing the presence, absence or intensity of the* [light] *generated by said* [light generating protein] *at various locations* [see above: "sites of inflammation"] *in said animal*, and further suggests *determining the expression of said endogenous promoter, via observing the presence, absence or intensity of the* [light] *generated by said* [light generating protein] *at various locations* [see above: "sites of inflammation"] *in a control laboratory animal which expresses said* [light generating protein] *under the direction of said promoter of said gene*, and further suggests *comparing the expression of said promoter determined in steps a) and b), wherein the expression determined in step a) is different from that in step b) when said test substance modulates said gene expression* (implicitly taught by the phrase "evaluated by their effects on induced luminescence in treated animals relative to control animals").

In addition, while the cited passage taught luciferase, Contag also taught as alternatives yellow fluorescent protein (column 3, lines 2-5; column 9, lines 29-32) and green fluorescent protein (column 9, lines 29-32).

In addition, Contag also clearly taught "mammals" (see title, abstract, column 2, lines 58-62, for example). More specifically, Contag taught non-human mammals (i.e. mice; see for example figures 5 and 6).

In addition, Contag taught (column 3, lines 25-30):

"If the image can be constructed in a time short relative to the time scale at which an "unimmobilized" subject moves, the subject is inherently "immobilized" during imaging and no special immobilization precautions are required. An image from the photon emission data is then constructed."

This passage clearly suggests a situation *wherein said animal is mobile and not restrained*.

With regard to the term "whole-body external fluorescent optical imaging", such term is explicitly defined in Applicant's specification (paragraph [0034] of the published application) as follows:

"As used herein, "whole-body external fluorescent optical imaging" refers to an imaging process in which the presence, absence or intensity of the fluorescence generated by the fluorophore at various locations in the host organism is monitored, recorded and/or analyzed externally without any procedure, e.g., surgical procedure, to expose and/or to excise the desired observing site from the host organism."

This definition is so broad as to encompass merely "looking" at the animal. Furthermore, neither this definition, nor anything in the claim, requires the "various sites" to be internal to the animal. In this regard, Contag taught (column 15, line 62):

"In cases where it is possible to use light-generating moieties which are extremely bright, and/or to detect light-emitting conjugates localized near the surface of the subject or animal being imaged, a pair of "night-vision" goggles or a standard high-sensitivity video camera, such as a Silicon Intensified Tube (SIT) camera (e.g.

Hamamatsu Photonic Systems, Bridgewater, N.J.), may be used. More typically, however, a more sensitive method of light detection is required."

Contag did not explicitly teach an embodiment where the method described at column 25, line 25 was performed wherein a) the animal was not restrained and b) green or yellow fluorescent protein was used in place of luciferase.

The central question here is one of a "reasonable expectation of success". Would there have been a reasonable expectation of success in studying potential anti-inflammatory compounds, as suggested by Contag, where the sites of inflammation were at or near the surface (e.g. the skin), using yellow or green fluorescent protein instead of luciferase?

Okabe taught transgenic mice expressing the green fluorescent protein (see entire article). Of note, Okabe stated (page 313, section 2.3): "The expression of EGFP in F1 pups from each transgenic founder mouse was examined by the naked eye or under a fluorescent microscope using excitation light." Also see caption, figure 1: "Although EGFP requires a blue excitation light (488 nm), emission of the green light was visible to the naked eye."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the EGFP taught by Okabe in place of the luciferase in the method described by Contag at column 25, line 25, for the purpose of studying potential anti-inflammatory compounds at sites of inflammation at or near the surface (e.g. the skin).

As Contag taught luciferase, yellow fluorescent protein and green fluorescent protein as equivalents for the purpose of his method, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute one for the other, thus arriving at the limitations *fluorescent protein*, *fluorescence*, *fluorophore*, and *autofluorescent* recited in claim 37. Furthermore, one would have been motivated to avoid restraining the animal, thus allowing its movement, in order to avoid placing unnecessary stress on the animal. Finally, one would have been motivated to substitute the EGFP taught by Okabe in place of the luciferase, as Okabe expressly stated (sentence spanning pages 315-316): "The great advantage of the GFP as a reporter is that the introduction of a substrate is not required, unlike other commonly used reporter genes such as beta-galactosidase, firefly luciferase, alkaline phosphatase, chloramphenicol acetyltransferase and beta-glucuronidase. This enabled us to observe the fluorescence from live cells and in intact form on a real-time basis." Whether one were to merely observe the mice with the naked eye, or use the "standard high-sensitivity video camera" suggested by Contag, either would qualify as "whole-body external fluorescent optical imaging".

Claim Interpretation

Claim 39 recites "administering a mutation-inducing agent or treatment to said laboratory animal" (wherein the animal is a non-human mammal). One interpretation is that this agent or treatment is administered to an animal *per se* (e.g. treating an animal with a chemical mutagen or radiation). Another interpretation is that an animal is genetically engineered to have the mutation (e.g. embryonic stem cells are treated with

a mutagen or a recombinant DNA molecule introducing a mutation into the genome, and implanted in the uterus to give rise to progeny offspring having the mutation). The following rejection of claim 39 under 35 U.S.C. 103(a) is made with regard to the second interpretation. A subsequent rejection under 35 U.S.C. 112, 1st paragraph is made with regard to the first interpretation. In addition, the phrase in step a) "while said animal is mobile and not restrained" is construed as pertaining to the "determining" phase, not to the "administering" phase.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin (US 6,380,458 prior art of record) in view of Contag et al (US 5,650,135 prior art of record) and Okabe et al (FEBS Letters 407:313-319; 1997).

Lin taught the creation of genetically modified zebrafish expressing green fluorescent protein (column 7, line 11: "A preferred reporter protein that can be directly detected is the green fluorescent protein (GFP).").

Lin also taught (column 11, lines 10-18):

"The disclosed transgenic fish can be used in combination with these and other mutations to assess the effect of a mutant gene on the expression of a gene of interest. For example, mutations can be introduced into strains of transgenic fish harboring an exogenous construct containing the expression sequences of a fish gene of interest operably linked to a sequence encoding a reporter protein. By comparing the expression of the reporter protein in fish with a mutation to those without the mutation,

the effect of the mutation on the expression of the gene from which the expression sequences are derived can be assessed."

Lin did not teach that the animals were non-human mammals, or that they were not restrained during observation.

Contag taught imaging light generating compounds including yellow and green fluorescent proteins (see abstract; column 9, lines 29-32).

In addition, Contag also clearly taught "mammals" (see title, abstract, column 2, lines 58-62, for example). More specifically, Contag taught non-human mammals (i.e. mice; see for example figures 5 and 6).

In addition, Contag taught (column 3, lines 25-30):

"If the image can be constructed in a time short relative to the time scale at which an "unimmobilized" subject moves, the subject is inherently "immobilized" during imaging and no special immobilization precautions are required. An image from the photon emission data is then constructed."

This passage clearly suggests a situation *wherein said animal is mobile and not restrained*.

With regard to the term "whole-body external fluorescent optical imaging", such term is explicitly defined in Applicant's specification (paragraph [0034] of the published application) as follows:

"As used herein, "whole-body external fluorescent optical imaging" refers to an imaging process in which the presence, absence or intensity of the fluorescence generated by the fluorophore at various locations in the host organism is monitored,

recorded and/or analyzed externally without any procedure, e.g., surgical procedure, to expose and/or to excise the desired observing site from the host organism."

This definition is so broad as to encompass merely "looking" at the animal. Furthermore, neither this definition, nor nothing in the claim, requires the "various sites" to be internal to the animal. In this regard, Contag taught (column 15, line 62):

"In cases where it is possible to use light-generating moieties which are extremely bright, and/or to detect light-emitting conjugates localized near the surface of the subject or animal being imaged, a pair of "night-vision" goggles or a standard high-sensitivity video camera, such as a Silicon Intensified Tube (SIT) camera (e.g. Hamamatsu Photonic Systems, Bridgewater, N.J.), may be used. More typically, however, a more sensitive method of light detection is required."

The central question here is one of a "reasonable expectation of success". Would there have been a reasonable expectation of success in substituting mice expressing GFP in place of the fish expressing GFP in the method taught by Lin?

Okabe taught transgenic mice expressing the green fluorescent protein (see entire article). Of note, Okabe stated (page 313, section 2.3): "The expression of EGFP in F1 pups from each transgenic founder mouse was examined by the naked eye or under a fluorescent microscope using excitation light." Also see caption, figure 1: "Although EGFP requires a blue excitation light (488 nm), emission of the green light was visible to the naked eye."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the EGFP expressing mice taught by Okabe

(and, correspondingly, an endogenous mouse promoter in place of a fish promoter) in place of the GFP expressing fish in the method described by Lin at column 11, lines 10-18, since one of ordinary skill in the art would have clearly recognized the equivalent use of mice in place of fish, and based on the disclosures of Okabe and Contag, one would have had a reasonable expectation of success in observing the effects of a genetically engineered mutation on a gene of interest in cases where the sites being observed were at or near the surface of the animal.

Furthermore, one would have been motivated to avoid restraining the animal, thus allowing its movement, in order to avoid placing unnecessary stress on the animal. Whether one were to merely observe the mice with the naked eye, or use the "standard high-sensitivity video camera" suggested by Contag, either would qualify as "whole-body external fluorescent optical imaging".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is made based on the first interpretation.

Under this interpretation, an animal *per se* is treated with a mutation-inducing agent. Treatment with mutagens, irradiation, etc for the purpose of inducing mutations was known in the art. Flaherty (Methods:A Companion to Methods in Enzymology 14:107-118 (1998)) taught (abstract): "Mouse mutations can be generated by a variety of techniques including those that rely on inducing agents such as X rays or chemicals and those that involve genetic manipulations such as in transgene insertions and gene knockouts…Inducing agents are often more efficient when random mutations in as yet unknown genes are desired." Here, "inducing agents" applies to the first interpretation of the phrase "administering a mutation-inducing agent or treatment to said laboratory animal" (see *Claim Interpretation* above), whereas "genetic manipulations" applies to the second interpretation.

Hence, treatments with "inducing agents" result in random mutations on a per cell basis; these treatments do not result in the simultaneous introduction of the same mutation in all or even more than one cell in the exposed subject.

Using this interpretation, then, what is required to enable claims 39 and 40 is the ability to observe a change in the fluorescence in a single mutated cell in a non-human mammal without restraining the animal. As a single cell is not visible to the naked eye, this would either require the use of a microscope, or require that the fluorescent signal from that single cell was so strong as to be detectable macroscopically. Alternatively, claims 39 and 40 would require the ability to control the mutation inducing agent in such a way as to mutate a sufficient number of cells in a sufficiently localized area of the animal (and also control *what* mutations were produced, i.e. those affecting the

expression of the fluorescent protein), so that a change in the fluorescent signal is macroscopically detectable without the need to immobilize the animal. It is respectfully submitted that none of these possibilities are enabled by Applicant's disclosure.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to imaging fluorescent protein signals in live animals in response to treatment with mutation inducing agents. The invention is the class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The breadth of the claims is not particularly relevant in this case.

Quantity of Experimentation

A great deal of experimentation would be required to practice the invention, given the technical issues discussed above and below. For, example, one would need to devise a way to control where and how a randomly acting mutation inducing agent

produced mutations. Or, one would need to develop a detector with sufficient sensitivity as to detect a single cell in an intact animal without restraining the animal. Or, one would need to develop a promoter:reporter system using a fluorescent protein with a sufficiently strong signal to allow macroscopic detection of the signal from a single cell.

The unpredictability of the art and the state of the prior art

Flaherty discussed the random nature of mutation inducing agents (abstract). It is self-evident that treating an animal with such agents would produce random mutations on a per cell basis. Assuming the animal recited in claims 39 and 40 has the endogenous promoter:fluorescent protein construct in every cell of its body, not every mutation so produced would be expected to result in a change in the level of expression of said fluorescent protein. One cannot control the particular mutations produced by these inducing agents, owing to their random nature, and not every mutation that occurred would be expected to affect the expression of the fluorescent protein. To observe any change in fluorescence in the treated versus untreated animals, either enough cells in a concentrated area would have to all be randomly mutagenized in such a way as to produce a detectable difference compared to the control animal, or the altered expression signal from a single cell would have to be so great as to allow detection without a microscope. Alternatively, the individual cells of the animal would need to be examined using a microscope, in which case the animal would need to be immobilized.

Yang et al (PNAS 97(3):1206-1211, Feb 2000, cited on the IDS of 04/22/2004), published one month prior to the instant application priority date and listing the inventors

as co-authors, discloses technology enabling the visualization of GFP expressing tumors in live mice. The article states (page 1210, paragraph spanning columns 1-2): "The minimum tumor size that could be imaged was a function of depth. The range of minimal size of GFP-expressing tumors that have been imaged externally thus far was from ~59 μm in diameter at a depth of 0.5 mm to ~1.86 mm in diameter at a depth of 2.2 mm in various tissues (Table 1)." The Yang disclosure does not say this limit of detection was for mice that were mobile and not restrained.

Working Examples

There are no working examples of this particular embodiment in the disclosure. There are also no working embodiments of detecting the signal from a single cell in a mobile animal.

Guidance in the Specification.

There is no guidance in the specification as to how one could control the mutations formed by the inducing agents such that sufficient numbers of cells in a particular location exhibit altered fluorescence so as to allow macroscopic detection in a mobile, unrestrained animal. Nor is there guidance as to how to produce a promoter:fluorescent protein reporter with sufficient fluorescence intensity so as to allow macroscopic detection of a single cell. Nor is there guidance has to how to place a mammal under a microscope so as to allow detection while at the same time the animal is mobile and unrestrained.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

The issue here is one of technical infeasibility. Because, as interpreted in this rejection, mutation inducing agents act randomly, any mutation having an effect on the expression of the fluorescent protein in the animal would occur on a purely cell-by-cell basis. Therefore, one could not compare the fluorescence of the mutated animal to the non-mutated animal by observing "various locations", or even at a single location, but only by observation on a cellular level. Applicant's disclosure does not enable this type of observation without immobilizing the animal (such as under a microscope, e.g.).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637